UNIVERSITY OF CALIFORNIA

DEPARTMENT OF BACTERIOLOGY
BERKELEY 4, CALIFORNIA

December 15, 1949

Dr. Joshua Lederberg
Department of Genetics
University of Wisconsin
Madison, Wisconsin

Dear Dr. Lederberg,

I am applying for a National Research Council Fellowship in the Natural Sciences and for an American Cancer Society Fellowship, in the hope that I may be succesful in obtaining one of these. I would like very much to use this fellowship to work in your laboratory during the period from September 1950 to June 1951.

I will receive my Ph.D. in Bacteriology at the University of California in June of 1950. I have been working under the directorship of Dr. R.Y. Stanier principally, and also with the aid of Drs. M. Doudoroff and H. Barker. I have held the position of Teaching Assistant in Bacteriology at this university for two years and now hold a Research Assistantship. For the past couple of years I have been investigating the phenomenon of mutation in Pseudomonas fluorescens, the preliminary work having been published in the Journal of Bacteriology, Vol. 58, 71, 1949.

The following will give you some idea of my recent work, and will indicate to you my fields of interest:

1. If one considers the mutation to the utilization of itaconate as a new mutation or a back mutation, it would be possible by continued selection of further mutations, to build a new catabolic pathway or at least uncover a lost catabolic process once possessed by the Pseudomonas. In addition, if this approach proved at all successful, one would have outlined the pathway of oxidative metabolism of some compound X and have demonstrated the feasibility of using this approach in the study of intermediary metabolism. This approach has been somewhat successful and I am now in the process of investigating the relationship between mesaconic acid (M) and itaconic acid (I) by use of the following mutants: I+ , I+ M+ .

2. On the basis of your theory of the economy of genes, it was thought that if the mutation to the utilization of itaconate is a novel function for a locus, a simultaneous loss of a more primitive function would have been evoked. With this in mind, together with the purpose of discovering the enzymatic nature of the itaconate mutation, metabolic studies of the itaconate mutant were undertaken. It was found by the method of simultaneous adaptation that the mutation to use itaconate results in a fundamental change in acetate metabolism. As a tool to the further study of itaconate utilization, use was made of a slow oxidizing mesaconate mutant which does not oxidize itaconate when this compound is present alone. Itaconate inhibits the oxidation of mesaconate and acetate, but does not inhibit the oxidation of succinate or fumerate. In fact, in the presence of any of the above mentioned dicarboxylic acids, itaconate itself is oxidized. The

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wild type is not inhibited by itaconate, nor is it used in the presence of succinate, fumerate or malate. The exact nature of this phenomenon requires further investigation.

To further elucidate the mechanism of mutation, chemical mutagenesis was attempted. In order to explain the occurrence of spontaneous mutation, a chemical was sought that occurs naturally, one that has been shown to be an intermediary metabolite, as well as having been implicated as a mutagen. Formaldehyde met these requirements. Experiments have definitely shown that formaldehyde is a mutagenic agent of a high order, and is characterized by a large degree of specificity. Formaldehyde induces an absolute increase of itaconate mutants in a resting population. Attempts to study the kinetics of the phenomena have so far resulted in failure, due to the reactivation of formaldehyde-deactivated cells by unknown components in the media. Formaldehyde will not induce mutation to streptomycin resistance in the Pseudomonas, nor will it induce mutation of E. coli to phage resistance. The nature of the reactivation process should be investigated and this may shed some light on the specificity of formaldehyde as a mutagenic agent.

I am interested in continuing these studies along lines which we could mutually decide upon. Of course, if you have some investigation under way or being contemplated that you would rather have me work on, I would be very happy to collaborate with you in such an undertaking.

I realize that the information given here is rather limited due to the shortage of time, but I hope that it is sufficient to enable you to make a favorable decision. If your decision is to accept me, would you please send me two letters, one addressed to the National Research Council, Washington, D.C., and the other to the American Cancer Society, Committee on Growth, National Research Council, Washington, D.C., stating that space is available for me at your laboratory and that you will act as my scientific advisor.

I would appreciate it very much if you would send me these letters as soon as possible, since I must turn in the applications by January 1, 1950.

Very truly yours,

Ellis Englesberg

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